REMARKS

Claims 1-29, 47-75, 78-81, 83-86, 88, 90, 92, 94, as amended and new claims 96-130 are pending in this application for the Examiner's review and consideration. Claims 30-46, 76-77, 82, 87, 89, 91, 93, and 95 were canceled.

The specification was amended to amend a typographical error wherein a hydrogen atom was inadvertently omitted from structure II.

Claim 1 was amended to correct a typographical error wherein the degree sign was not properly placed after temperatures. Claim 1 was also amended to more clearly recite the invention. Claim 15 was amended to delete the feature that the quantity of solvent is such that when the solvent is combined with the lyophilized epothilone the resulting solution contains from about 2 mg/mL to about 4 mg/mL of said analog (*See, e.g.*, Specification, page 14, lines 24-29) and to more clearly recite the invention. This feature now is recited in new claim 103. Claims 24-26 were amended to include the term "infusion" (*See, e.g.*, Specification, page 16, lines 3-4). Claim 47 was amended to recite that the compound of formula I is lyophilized (*See, e.g.*, Specification, page 13, lines 15-18 and page 19, lines 17-18). Claims 51 and 73 were amended to be written in independent form. Claim 39 was simply amended to replace the term "infusing" with --administering-- (*See, e.g.*, Specification, page 13, lines 15-18 and page 19, lines 17-18). Claim 83 was amended to include the features of canceled claims 88, 90 and 92. Claim 85 was amended to depend from claim 84. Claim 86 was amended to recite that the compound of formula I is administered every 3 weeks (*See, e.g.*, Specification, page 20, lines 1-3). New claims 96-98 recite embodiments wherein the lyophilized epothilone analog of claims 1, 15 and 16 is free of excipients (*See, e.g.*, Specification, page 14, lines 18-23). New claims 99 and 100 are similar to claims 18-20 but depend from new claims 97 and 98, respectively. New method claims 101 and 102 are similar to method claims 51 and 52 but recite that the compound used in the methods is the compound [1S-[1R*, 3R*(E), 7R*, 10S, 11R*, 12R*, 16S*]]-7, 11-dihydroxy-8,8,10, 12, 16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0] heptadecane-5, 9-dione (*See, e.g.*, Specification, page 2, line 22 to page 3, line 2). New claims 104-130 replace canceled claims 30-46. New independent claim 104 is the same as canceled claim 30 except that it only recites intravenous administration and includes the feature that the epothilone is administered for 3 days daily or for 5 days daily (*See e.g.*, Specification, page 19, lines 17-20). New independent claim 118 is the same as canceled claim

30 except that it only recites intravenous administration and includes the feature that the epothilone is administered every week or every 3 weeks (*See e.g.*, Specification, page 20, lines 1-3). No new matter is added by these claim amendments and new claims so that its entry at this time is warranted.

SUMMARY OF THE INVENTION

The present invention is directed to a process for formulating an epothilone analog[1] of formula (I) for parenteral administration (claims 1-14 and 96-98); pharmaceutical preparations comprising, in separate vials, a lyophilized epothilone analog of formula (I) and a solvent comprising a mixture of about equal parts by volume of dehydrated alcohol and a nonionic surfactant, such that when the contents of the vial are combined the resulting solution contains about 2 mg/mL to about 4 mg/mL of the epothilone analog (claims 15-17 and 97-100); a process for forming a pharmaceutical composition for parenteral administration comprising mixing the contents of the vials recited in claims 15-17 to provide a solution and diluting the resulting solution with a parenteral diluent (claims 18-23 and 99-100); a method for treating a patient with an epothilone analogue of formula I by administering to the patient the composition recited in claims 18-20 (claims 24-29); a pharmaceutical composition for parenteral administration comprising an epothilone compound of formula I, dehydrated alcohol, and a nonionic surfactant (claims 47-51); methods of treating cancer in a patient comprising administering the composition of claim 47 (claims 52-68 and 101-102); methods of treating cancer while avoiding neurotoxicity which comprises intravenously infusing a therapeutically effective amount of a compound of formula I over a period of about 1 hour (claims 69-82); a method of treating cancer in a patient comprising intravenously or orally administering an epothilone compound of formula I (claims 83-84, 88, 90, 92, and 94); and a method for treating cancer in a patient with an epothilone analogue of formula I by administering to the patient the epothilone analogue of formula (I) intravenously (claims 104-130).

THE REJECTION UNDER 35 U.S.C. §103(A) SHOULD BE WITHDRAWN

Claims 1-95 are rejected under 35 U.S.C. §103(a) as being obvious over U. S. patent no. 6,387,927 to Altmann et al. ("Altmann") or U. S. published application no. US

[1] Applicants point out that the term "epothilone analog" is defined in the instant specification at page 2, lines 1-3.

2002/0045609 to Ashley et al. ("Ashley") for the reasons set forth on page 2 of the Office Action. Applicants respectfully traverse the rejection. In sum, the compounds encompassed within the instant claims are neither disclosed nor suggested by the cited references, as discussed in detail below.

As the Examiner is well aware the proper inquiry for obviousness is whether the references disclose each and every feature of the claim (*See, e.g.*, MPEP, 1242) and whether the references suggest the invention and provides one of ordinary skill in the art with a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991); *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Neither Altmann nor Ashley render the present claims obvious since neither of the references (a) discloses each and every feature of the invention and (b) fails to provide a reasonable expectation of success.

Altmann discloses a specific class of benzoazolyl substituted epothilone derivatives, the production of these compounds and new intermediates, pharmaceutical preparations containing these compounds, and the use of the compounds in the treatment of warm-blooded animals, or their use in the production of pharmaceutical preparations for the treatment of warm-blooded animals (*See, e.g.,* Altmann, column 1, lines 9-15). The compounds have the structure depicted in Altmann at column 2, line 22 to column 3, line 15.

Altmann cannot render the present claim obvious since Altmann does not disclose or suggest each and every feature of the claims nor provide the legally required suggestion or expectation of success to modify Altmann to arrive at the claimed methods. For example, Altman does not disclose or suggest the lactam compounds of formula I as recited in the currently pending claims. The compounds disclosed in Altmann are completely different from the compounds of formula I in at least two respects. First, the compounds disclosed in Altmann all have a benzoazolyl substituent at the C-15 position of the epothilone ring wherein the phenyl ring of a benzoazolyl system is directly bonded to C-15 of the epothilone ring. In contrast, the compounds of formula I have an R_6 substituent at the C-15 position of the epothilone ring that is directly bonded to a carbon-carbon double bond that is then further attached to other substituents. Second, the present claims are directed to a genus of *lactam* compounds. Although, Altmann generically teaches a genus that includes both lactones and lactams, each and every example in Altmann is a lactone compound. Thus, Altmann actually *teaches away* from lactams by focusing on lactones and by focusing on epothilone A and epothilone B which they wish to mimic and

which are lactones.[2] Indeed Altmann clearly states that lactones are preferred (*See, e.g.*, Altmann, column 9, lines 11-13 and column 10, lines 36-38). Moreover, Altmann has no examples of a lactam. There is no disclosure or suggestion in Altmann of a compound of formula I, much less formulations comprising a compound of formula I, or methods of treating patients with a compound of formula I. Accordingly, Altmann cannot render the currently pending claims obvious.

In addition to failing to disclose or suggest the compounds of each of the claims presented herein, Altmann fails to disclose or suggest one or more elements of each of the following claims:

Claims 1-14: There is absolutely no disclosure or suggestion in Altmann of the process steps recited in independent claim 1 for the production of a parenteral composition. Indeed, Altmann does not disclose or suggest any process to formulate a lyophilized epothilone analog for parenteral administration. The claimed method advantageously allows the epothilone analogs, which have poor wetting characteristics, to be solubilized so that the resulting solution can be lyophilized to provide an amorphous epothilone compound while also minimizing degradation of the epothilone analog (*See, e.g.*, Specification, page 13, lines 19-27). Altmann provides no reasonable expectation that the claimed process would successfully provide an amorphous epothilone compound that can be readily solubilized while minimizing degradation of the epothilone compound.

Claims 15-23: Altmann also does not render independent claim 15 and dependent claims 16-23 obvious. There is no disclosure or suggestion in Altmann of a pharmaceutical preparation that comprises, in separate vials, a lyophilized epothilone analog of formula I and a quantity of solvent, wherein the solvent comprises a mixture of about equal volumes of dehydrated ethanol and a nonionic surfactant, as recited in independent claim 15. Altmann only discloses combining his epothilone compounds in neat, *i.e.*, 100 percent, polyethylene glycol 300 (PED 300) (*See, e.g.*, Altmann, column 30, lines 10-17 and column 96, lines 18-22). Using about equal volumes of dehydrated ethanol and a nonionic surfactant as a solvent for the epothilone analogue, however, advantageously provides a solution that can then be combined with a diluent for intravenous administration while minimizing the amount of solvent and,

[2] These arguments should not be construed as an admission that Altmann enables lactone compounds.

accordingly, minimizing adverse reactions from exposure to the solvent when the intravenous formulation is administered to a patient (*See, e.g.*, Specification, page 15, lines 18-25).

Furthermore, Altmann does not render new claim 103 obvious. New claim 103 recites the feature that the quantity of solvent is an amount such that when the solvent is combined with the lyophilized epothilone the resulting solution contains from about 2 mg/mL to about 4 mg/mL of said analog. Altmann only discloses solutions of epothilone compounds in a solvent that have concentrations of 1 mg/mL (*See, e.g.*, Altmann, column 96, lines 18-22). A concentration of 1 mg/mL is significantly less concentrated than the concentration of about 2 mg/mL to about 4 mg/mL that is provided by the claimed pharmaceutical preparation. By providing a more concentrated solvent, the claimed pharmaceutical preparation, when diluted with a diluent for intravenous administration, provides an infusion solution that will have less solvent per mg of epothilone analog in the infusion solution, and accordingly, will reduce adverse reactions from exposure to the solvent when the intravenous formulation is administered to a patient (*See, e.g.*, Specification, page 15, lines 18-25). Clearly, there is no disclosure or suggestion in Altmann of a pharmaceutical preparation that comprises the specific epothilone compound recited in claim 16.

Claims 24-29: There is no disclosure or suggestion in Altmann to use the formulations recited in claims 15-23 in a method to treat a patient as recited in claims 24-29. As discussed above, using the formulations of the invention to treat a patient advantageously minimizes adverse reactions from exposure to the solvent (*See, e.g.*, Specification, page 15, lines 18-25). Not only does Altmann fail to disclose or suggest the epothilone compounds used in the claimed methods, Altmann also fails to provide the required expectation that the epothilone compounds of formula I would be effective for treating patients. Clearly, there is no disclosure or suggestion in Altmann of a method that uses the specific epothilone compound recited in claim 25 to treat a patient.

Claims 30-46: The rejection of claims 30-46 is rendered moot by the cancellation of these claims. New claims 104-130 replace canceled claims 30-46. Accordingly, Applicants will address the rejection with respect to new claims 104-130. There is no disclosure or suggestion in Altmann of a method for treating cancer comprising intravenously administering to a patient an epothilone compound of formula I daily for 3 days or daily for 5 days, as recited in independent claim 104, or intravenously administering to a patient an epothilone compound of

formula I weekly or every 3 weeks, as recited in independent claim 117. Also, as discussed above, the epothilone compound of formula I recited in these claims is structurally distinct from the compounds specifically disclosed in Altmann.

Claims 47-68: There is no disclosure or suggestion in Altmann of a pharmaceutical composition that comprises a compound of formula I, dehydrated alcohol, and a non-ionic surfactant as recited in independent claim 47, as amended. There is also no disclosure or suggestion in Altmann of the methods of treating cancer recited in dependent claims 52-68 that involve administering the pharmaceutical composition of claim 47 that comprises the specific epothilone compound of formula I, which is a lactam. The claimed pharmaceutical compositions have good stability and, when formulated for parenteral administration to a patient, have a low incidence of adverse reactions (*See, e.g.,* Specification, page 15, lines 16-25).

Claims 69-74: The compounds specifically disclosed in Altmann are lactones whereas those in the claimed methods are lactams and there is absolutely no disclosure or suggestion in Altmann to treat cancer with a compound of formula I or to administer an epothilone compound intravenously over a period of about 1 hour. By administering the recited epothilone compound over 1 hour the method of the invention advantageously reduces or avoids neurotoxicity.

Claims 75-82: The rejection of claims 76-77 is rendered moot by the cancellation of these claims. With regard to the other claims, as noted above, the compounds specifically disclosed in Altmann are lactones whereas those in the claimed methods are lactams and there is no disclosure or suggestion in Altmann of a method for treating cancer that comprises administering to a patient an epothilone analog, much less an epothilone analog of formula I, in a 4 week dosing cycle that comprises 3 weeks of weekly intravenous administration and one week of oral administration.

Claims 83-95: The rejection of claims 87, 89, 91, 93, and 95 is rendered moot by the cancellation of these claims. With regard to the other claims, as discussed above, the epothilone compound of formula I recited in these claims is structurally distinct from the compounds disclosed in Altmann. Moreover, there is no disclosure or suggestion in Altmann that an epothilone compound of formula I could be used to treat cancer in a patient. Clearly, there is no disclosure or suggestion in Altmann of the specifically recited administration protocol

wherein the epothilone compound of formula I is administered orally to a patient daily for 3 days, daily for 5 days, or weekly. Finally, Altmann provides no reasonable expectation that a compound of formula I would be effective at treating cancer.

Ashley, also does not render the claims obvious. Ashley discloses epothilone derivatives useful for treating cancer and other conditions characterized by abnormal cellular proliferation in a subject in need thereof (*See, e.g.,* Ashley, page 1, paragraph 15). The compounds have the structure depicted at page 4, paragraph 42 of Ashley.

Ashley cannot render the present claim obvious since Ashley does not disclose or suggest each and every feature of the claims or provide the legally required suggestion or expectation of success to modify Ashley to arrive at the claimed methods. For example, Ashley simply teaches a general genus of compounds that encompasses both lactones and lactams but then actually teaches away from lactams by focusing on epothilone A and epothilone B which they wish to mimic and which are lactones. In contrast, the present claims are directed to a specific genus that only encompasses *lactam* compounds.

In addition to failing to disclose or suggest the compounds of each of the claims presented herein, Ashley fails to disclose or suggest one or more elements of each of the following claims:

Claims 1-14: Ashley, like Altmann, does not render independent claim 1 or dependent claims 2-14 obvious since there is no disclosure or suggestion in Ashley of the process recited in independent claim 1 for formulating an epothilone analog for parenteral administration, that includes each of the recited steps. Indeed, Ashley is completely silent on methods for formulating epothilone compounds for parenteral administration. As noted above, the claimed method advantageously allows the epothilone analogs, which have poor wetting characteristics, to be solubilized so that the resulting solution can be lyophilized to provide an amorphous epothilone compound while also minimizing degradation of the epothilone analog (*See, e.g.,* Specification, page 13, lines19-27). There is simply no disclosure or suggestion in Ashley of the process claimed in independent claim 1 or, for that matter, any process for lyophilizing an epothilone compound. Moreover, Ashley does not provide a reasonable expectation that the claimed process would successfully solubilize an epothilone compound while also minimizing

degradation of the epothilone compound to provide a solution that can than be lyophilized to provide an amorphous form of an epothilone compound.

Claims 15-29: There is no disclosure or suggestion in Ashley of the pharmaceutical preparation that comprises, in separate vials, a lyophilized epothilone analogue and a quantity of solvent, wherein the solvent comprises a mixture of about equal volumes of dehydrated ethanol and a nonionic surfactant, as recited in independent claim 15. Although, Ashley discloses in Example 35 a formulation wherein an epothilone analog is combined with dehydrated ethanol and a nonionic surfactant, there is no disclosure of the epothilone analog being lyophilized. Using a lyophilized epothilone advantageously provides a stable form of the epothilone that avoids rapid degradation of the epothilone analog from contact with water (*See, e.g.,* Specification, page 13, lines 11-18). Clearly, there is no disclosure or suggestion in Ashley of a pharmaceutical preparation wherein the specific epothilone analog is the epothilone analog recited in dependent claim 16. Similarly, there is no disclosure in Ashley of a process for making a pharmaceutical composition or a method for treating a patient, wherein the epothilone analog used in the process or method of treating comprises the specific epothilone analog recited in dependent claim 16, as recited in dependent claims 19 and 25, respectively.

Claims 30-46: The rejection of claims 30-46 is rendered moot by the cancellation of these claims. New claims 104-130 replace canceled claims 30-46. Accordingly, Applicants will address the rejection with respect to new claims 104-130. Although, Ashley discloses that oral and intravenous administration can be used to administer epothilone compounds, there is no disclosure or suggestion of a method for treating cancer comprising intravenously administering to a patient an epothilone compound of formula I daily for 3 days or daily for 5 days, as recited in independent claim 104, or intravenously administering to a patient an epothilone compound of formula I weekly or every 3 weeks, as recited in independent claim 117. Moreover, as discussed above, the epothilone compound of formula I recited in these claims is structurally distinct from the compounds specifically disclosed in Ashley.

Claims 47-68: There is no disclosure or suggestion in Ashley of a pharmaceutical composition that comprises a compound of formula I, dehydrated alcohol, and a non-ionic surfactant as recited in independent claim 47, as amended. There is also no disclosure or suggestion in Ashley of the methods of treating cancer recited in dependent claims 52-68 that involve administering the pharmaceutical composition of claim 47 that comprises the specific

epothilone compound of formula I, which is a lactam. The claimed pharmaceutical compositions have good stability and, when formulated for parenteral administration to a patient, have a low incidence of adverse reactions (*See, e.g.,* Specification, page 15, lines 16-25).

Furthermore, independent claim 47, as amended, recites that the compound of formula I is present in lyophilized form. As noted above, there is no disclosure or suggestion in Ashley of a pharmaceutical composition for parenteral administration wherein the epothilone analog is lyophilized. Using a lyophilized epothilone analog, however, advantageously avoids degradation of the epothilone analog that results from contact with water (*See, e.g.,* Specification, page 13, lines 11-18). Clearly, there is no disclosure or suggestion in Ashley of a pharmaceutical composition that comprises the specific compound recited in independent claim 51.

Claims 69-74: The compounds specifically disclosed in Ashley are lactones whereas those in the claimed methods are lactams and there is absolutely no disclosure in Ashley to treat cancer with a compound of formula I, which is a lactam, or to administer an epothilone compound over a period of about 1 hour.

Claims 75-82: The rejection of claims 76-77 is rendered moot by the cancellation of these claims. With regard to the other claims, although, Ashley discloses a variety of routes of administration for epothilone compounds, including intravenous administration and oral administration, there is no disclosure or suggestion in Ashley of a method for treating cancer that comprises administering to a patient an epothilone analog, much less an epothilone analog of formula I, in a 4 week dosing cycle that comprises 3 weeks of weekly intravenous administration and one week of oral administration.

Claims 83-95: The rejection of claims 87, 89, 91, 93, and 95 is rendered moot by the cancellation of these claims. With regard to the other claims, as discussed above, the epothilone compound of formula I recited in these claims is structurally distinct from the compounds disclosed in Ashley. Moreover, there is no disclosure or suggestion in Ashley that an epothilone compounds of formula I could be used to treat cancer in a patient. Clearly, there is no disclosure or suggestion in Ashley of the specifically recited administration protocol wherein the epothilone compound of formula I is administered orally to a patient daily for 3 days, daily for 5 days, or weekly. Furthermore, Ashley provides no reasonable expectation that a compound of formula I would be effective at treating cancer.

For the above reasons, Applicants respectfully request that the rejection of claims 1-95, under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants believe the application is in condition for allowance and earnestly requests reconsideration of the claims and allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

A fee of $522.00 is believed to be due for the addition of three (3) independent claims in excess of three (3) and for the addition of fifteen (15) new claims. Please charge these and any other required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: July 3, 2003

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